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Award Number: DAMD17-01-1-0275

TITLE: Breast Cancer Risk in Relation to Serum IGF-1, IGFBP-3,

and Their Genetic Determinants: A Study Within the

European Prospective Into Cancer (EPIC)

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REPORT DATE: September 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE

September 2003

3. REPORT TYPE AND DATES COVERED

Annual (1 Sep 2002 - 31 Aug 2003)

4. TITLE AND SUBTITLE

Breast Cancer Risk in Relation to Serum IGF-1, IGFBP-3, and Their Genetic Determinants: A Study Within the European Prospective I.nto Cancer (EPIC)

5. FUNDING NUMBERS

DAMD17-01-1-0275

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U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

8. PERFORMING ORGANIZATION REPORT NUMBER

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

<u>Purpose and scope</u>: We are conducting a large case-control study nested within a prospective cohort, to estimate relative risks of breast cancer by serum levels of IGF-I and IGFBP-3, and to examine associations of polymorphisms in 15 candidate genes with levels of IGF-I, IGFBP-3, and cancer risk.

Progress report: in the first two years of this project, 1084 breast cancer cases and 2116 control subjects were included in the study, and measurements of IGF-I and IGFBP-3 were (practically) completed. A first series of 23 SNPs were typed for all case and control subjects, and typing of 18 additional SNPs is ongoing.

Major findings: Elevated serum IGF-I shows a moderate increase in breast cancer risk among postmenopausal women. Preliminary analyses also show significant associations of a number of SNPs and haplotypes with IGF-I, IGFBP-3, or breast cancer risk.

14. SUBJECT TERMS Breast cancer, epidemi	iology, genetics, insul	in-like growth factor I	15. NUMBER OF PAGES 31
-			16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

IGF-I is a central hormone in the regulation of anabolic (growth) processes as a function of available energy and elementary substrates (e.g., essential amino acids), and has strongly mitogenic and anti-apoptotic activities. Results from *in vitro* studies and animal experiments show that, in excess, the anabolic signals by IGF-I can promote the development of tumors at various organ sites, and recent epidemiological studies have shown an increased breast cancer risk in women with elevated serum IGF-I, or with elevated levels of IGF-I for given levels of IGFBP-3, the major plasmatic IGF-binding protein.

While nutritional status is one important determinant of circulating IGF-I levels (Kaaks & Lukanova, 2001), heritability studies have shown that, in well-nourished populations, a large part (40-60 %) of variation in IGF-I is (co)determined by genetic factors (Harrela et al., 1996; Hong et al. 1996; Verhaeghe et al., 1996). To increase understanding of what are the major determinants of IGF-I levels, as well as cancer risk, we conduct a study with the following objectives:

- 1. Confirm that elevated prediagnostic serum levels of IGF-I increase breast cancer risk, especially in premenopausal women;
- 2. Describe exhaustively existing polymorphisms, allele frequencies and haplotypes in 15 selected genes related to the secretion of growth hormone, and hence to the synthesis of IGF-I and IGFBP-3; and
- 3. Examine whether these genetic polymorphisms are related to significant increases or decreases in circulating levels of IGF-I and IGFBP-3, as well as in breast cancer risk.

Our project is a large case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), using prediagnostic blood (serum and DNA) samples collected during 1992-1998, from 233,800 women in western Europe.

As mentioned in our original application, the study was planned in four parts:

- 1. A case-control study (about 1000 cases and 1000 controls) nested in a prospective cohort, to estimate the associations of serum IGF-I and IGFBP-3 levels with breast cancer risk;
- 2. Preparation of an exhaustive catalogue of polymorphisms and haplotypes in the 15 selected candidate genes, and a ("phase-1") association study on a subset of 400 controls to identify genotypes that have a minimum level of association with serum of IGF-I and IGFBP-3;
- 3. A nested case-control study, to estimate relative risks of breast cancer in relation only to those genotypes selected in phase-1;
- 4. A ("phase-2") study of associations of these selected genotypes with IGF-I and IGFBP-3, in all cases and controls.

BODY

For <u>Year 1</u>, our workplan (as in the "Statement of Work" section of our application), was as follows:

- 1. Selection of cases and controls, using the established eligibility and matching criteria, and extraction of case-control data sets with relevant information from questionnaires and anthropometry: **Task 1, months 1-2**.
- 2. Retrieval of serum and buffy coat samples from the central EPIC storage facility; assembly of the serum samples into batches of matched case-control sets for immunoassays; assembly of the buffy-coat samples into batches for DNA extraction: Task 2, months 2-4.
- 3. Assays of IGF-I and IGFBP-3 serum of breast cancer cases (n = 1000) and controls (n = 1000): Task 3, months 7-12.
- 4. DNA extraction for all 2000 cases and controls: Task 5, months 1-12.
- 5. Preparation of an exhaustive catalog of polymorphisms by searching the literature, and by DHPLC analysis of DNA from a subset of 200 subjects: **Task 6: months 1-12**.

As described in our previous report (Year 1), we achieved most of these goals in Year 1, whereas for some other tasks we were in advance of our planned schedule. The following list provides a quick recapitulation of key accomplishments in Year 1:

- a) <u>Case-control selection, DNA extraction, and growth factor measurements:</u>
 - An almost complete selection of breast cancer cases (n=810) and control subjects (n=1620) within the EPIC cohorts, for the nested case-control study on serum IGF-I, IGFBP-3 and breast cancer risk;
 - Measurement of IGF-I and IGFBP-3 for these cases and controls;
 - DNA extraction for these cases and controls;
- b) <u>Preparation of SNP genotyping tools</u>:
 - Identification of a comprehensive catalogue of >120 (possible) single nucleotide polymorphisms (SNPs) in all candidate genes included in the present study;
 - Preparation of a DNA genotyping chip, for 78 of these polymorphisms that had confirmation of being true polymorphisms;
- c) Preliminary genotyping study:
 - A first descriptive study of SNP and haplotype frequencies for all candidate genes, in a population of 477 subjects (women plus men); and
 - A preliminary analysis of associations of SNPs and circulating levels of IGF-I and IGFBP-3 (corresponds to **Task 7**, originally planned for Year 2);
 - Selection of a first series of 23 SNPs to be typed in the full case-control study, using the Taqman assay.

During <u>Year 2</u>, we completed some of the tasks originally planned for Year 1. In particular, we included 274 cases of breast cancer and 496 control subjects, for whom questionnaire information available in 2002 did not allow proper control matching (this information arrived during 2002). Thus, total numbers of breast cancer cases and control subjects were brought to 1084 and 2116, respectively.

For these additional study subjects, DNA was extracted from their stored buffy coat specimens, and additional serum measurements of IGF-I were performed. For IGFBP-3, measurements were delayed because of technical difficulties with the (commercial) assay, due to complications at the manufacturing site (DSL, TX, USA). In collaboration with the company, these problems have now been solved, and completion of the IGFBP-3 assays is scheduled for September-October 2003.

Tasks planned for Years 2 and 3 ("Statement of Work" section of our study proposal) were:

- 6. Statistical analysis of the nested case-control study, relating breast cancer risk to prediagnostic serum levels of IGF-I and IGFBP-3 (**Task 4, months 13-24**);
- 7. Complete genotyping of a subset of 200 breast cancer cases and 200 control subjects; Statistical analysis of phase-1 association study, relating genotypes to serum concentrations of IGF-I and IGFBP-3 (Task 7; months 12-24); and
- 8. Genotyping of the remaining 1600 cases and controls, for a limited set of polymorphisms, selected in phase 1;

Statistical analysis of associations between polymorphisms, serum levels of IGF-I and IGFBP-3, and breast cancer risk; Writing of reports (**Task 8**; months 24-36).

All of the goals up to the end of Year 2, and much of the goals for Year 3, have been met:

(a) Statistical analysis of breast cancer risk in relation to prediagnostic serum levels of IGF-I and IGFBP-3 (Task 4):

Although IGFBP-3 measurements are not complete yet (see above), we performed extensive statistical analyses of the relationships of breast cancer risk with serum IGF-I and IGFBP-3 concentrations. These analyses showed no clear relationship of breast cancer risk with IGF-I among women who were premenopausal at the time of blood donation, contrary to findings from some previous cohort studies. Among postmenopausal women, however, there was a moderate association of risk with IGF-I (relative risk of about 1.5 between the extreme quintiles of the IGF-I exposure distribution).

(b) Further SNP genotyping of breast cancer cases and control subjects (Task 8):

For all 1084 breast cases and 2116 controls included in th nested case-control study, a first series of 23 SNPs were typed by Taqman. For an additional number of SNPs, genotyping assays by the Taqman technique did not work (a normal observation with this type of assay); for these, we are currently trying to set up alterantive assays (e.g., "Amplifluor"). For yet another set of SNPs, our DNA chip initially used for genotyping in a smaller subset of individuals (total of 78 SNPs) did not give valid

results, and we were thus unable not confirm whether or not polymorphic alleles were prevalent enough to make their measurement worthwhile. For this latter subset, we have now decided to type all of these SNPs by Taqman or the Amplifluor technique. In total, some 18 SNPs remain to be typed for all case and control subjects, which will bring the total number of SNPs typed to 41. This total number of assays (SNPs) is considerably larger than that foreseen in our original study proposal; however, genotyping of this increased number largely has become possible due to the progressive reductions in genotyping reagent costs.

(c) Statistical analysis of SNP / haplotype associations with IGF-I and IGFBP-3 (Tasks 7 and 8):

In Year 1, performed preliminary statistical analyses were performed to examine possible associations of SNPs and their haplotypes with serum concentrations of IGF-I and IGFBP-3, within a first series of 477 subjects (see our previous report). During Year 2, we re-analysed our much more extensive data, from all 1084 breast cancer cases and 2116 controls, using the same methods as in Year 1. Analyses were performed with a variety of statistical models, of increasing completeness and complexity:

- <u>at the level of individual SNP loci</u>: associations of alleles with IGF-I and IGFBP-3 concentrations were estimated under assumption of dominance, codominance, or recessiveness of alleles.
- <u>at the level of full gene loci</u>: individuals' most likely haplotypes were estimated, and individuals' haplotype combinations (of the two chromosomes) were associated with IGF-I and IGFBP-3 levels; in further analysis, haplotypes were transformed into SNP genotypes sorted by parental phase, and generalized linear models (GLM) were used to relate phenotype (IGF-I, IGFBP-3) to these phased genotype variables, plus their possible interaction terms within a gene (following an approach described by Cordell and Clayton, 2001).

During <u>Year 2</u>, we have also been working further on refinements of the statistical analysis procedures, implementing several new procedures (programmed in SAS), and testing different existing programs for estimation of haplotypes ('Arlequin'; 'PHASE'; 'SAS-Genetics'; TagSNP). A final analysis will be performed when genotyping of all 41 SNPs will be completed (planned to be complete by the end of 2003). Only after completion will it be possible to estimate full haplotypic variation at gene loci, and to perform definitive analyses.

Preliminary analyses of Year 1 suggested that up to some 20% of the total between-subject variation in IGF-I levels might be explained by measured genetic polymorphisms. This percentage was most likely overestimated, due to a comparatively small study size and over fitting of statistical models. Our current analyses, based on much larger numbers of observations, show smaller, but probably more realistic effects of SNPs and/or haplotypes on serum IGF-I and IGFBP-3 levels. Amongst the most significant associations was the relationship of IGFBP-3 levels with SNPs in the IGFBP-3 gene, which has also been observed in other studies (Jernström et al., 2001).

(d) <u>Statistical analysis of SNP / haplotype associations with breast cancer risk (Task 8)</u>:

Preliminary statistical analyses have been performed, using logistic regression models to relate breast cancer risk to SNP genotypes as well as to haplotypes. The analytical strategy is similar to that for the analysis in relation to serum IGF-I and IGFBP-3 concentrations (described above). In addition, we have implemented a series of models to estimate haplotype relative risks, for a haplotype 'dosage' estimated as posterior probability for each of the possible haplotypes given SNP genotypes (following methods described by Stram et al., 2003).

A definitive statistical analysis of breast cancer risk in relation to SNP genotypes and, especially, haplotypes will be possible only after completion of genotyping for all 41 SNPs (by the end of 2003).

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments in Year 2 were:

- Inclusion in the study of 274 additional breast cancer cases and 496 additional control subjects, bringing the total number of cases and controls to 1084 and 2116, respectively;
- DNA extraction and genotyping of a first series of 23 SNPs, for all cases and controls;
- IGF-I measurements for all cases and controls; nearly complete measurements of IGFBP-3.
- Extensive preliminary statistical analyses of associations between breast cancer risk, prediagnostic serum levels of IGF-I and IGFBP-3, and SNP and haplotype data;
 Preparation of programs and SAS macros for all analytical steps, ready to be implemented when all laboratory analyses will be completed.

PLAN FOR YEAR 3

Plans for Year 3 are as follows:

- Completion of genotyping of the 18 additional SNPs identified, and selected for the study;
- A definitive statistical analysis of the complete SNP genotype and haplotype data, in relation to serum IGF-I and IGFBP-3, as well as breast cancer risk;
- Preparation of articles, to report all major findings in scientific journals.

REPORTABLE OUTCOMES

None, so far. First drafts of articles are in preparation; these will be finalized after completion of all laboratory assays for genotypes and IGFBP-3, and definitive statistical analysis.

CONCLUSIONS

Our study is ahead of schedule, and actually has been expanded to include a larger number of SNP assays than initially foreseen (made possible because of decreasing genotyping costs). Results so far do indicate a number of associations of IGF-I, IGFBP-3 and breast cancer risk with SNP genotypes and/or haplotypes for full gene loci. The overall proportion of between-person variance in circulating levels of IGF-I and IGFBP-3 explained by the genetic polymorphisms is modest, however, but is still based on rather incomplete SNP and haplotype data.

Elevated serum IGF-I concentrations show a modest increase in breast cancer risk, but only among postmenopausal women.

Final statistical analyses of associations between breast cancer risk in relation to IGF-I, IGFBP-3, and genetic variants will be performed in Year 3, after the completion of the IGFBP-3 assays and additional SNP genotyping.

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APPENDICES

Tables with preliminary results from statistical analyses

Figure 1. Relative risk of breast cancer by quintiles of growth hormone levels

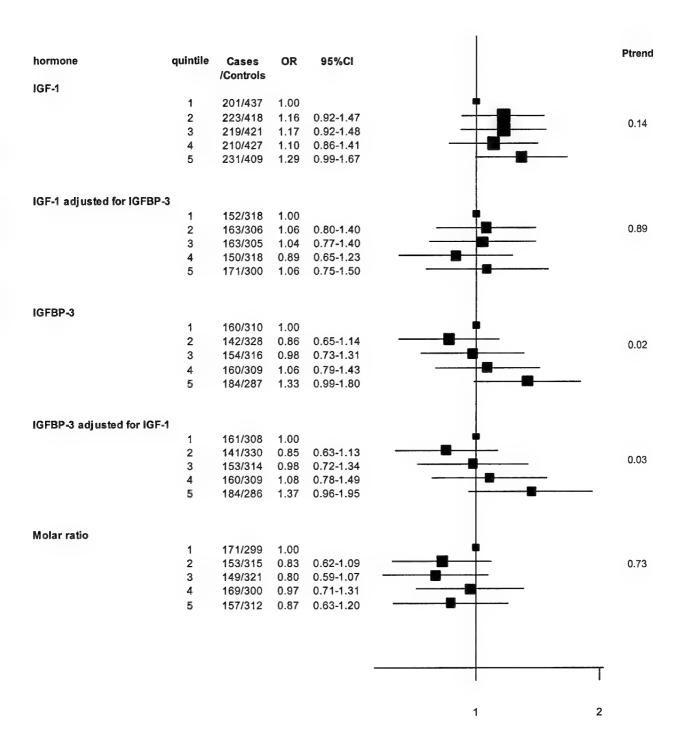


Figure 2. Relative risk of breast cancer among premenopausal women by quintiles of growth hormone levels

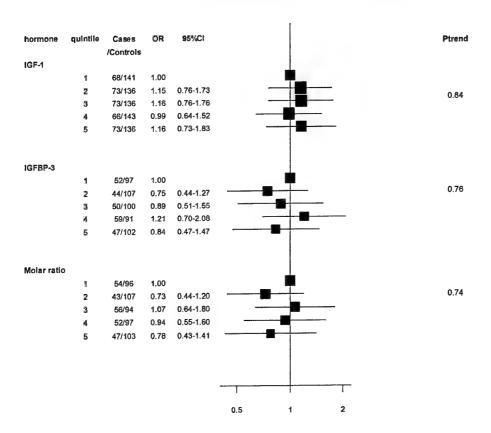


Figure 3. Relative risk of breast cancer among postmenopausal women by quintiles of growth hormone levels

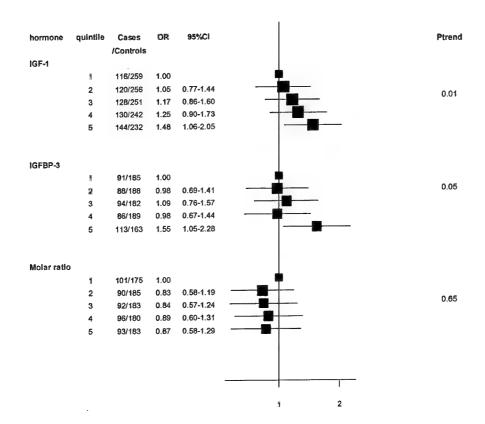


Figure 4. Relative risk of breast cancer among women younger than 50 at diagnosis at diagnosis by quintiles of growth hormone levels

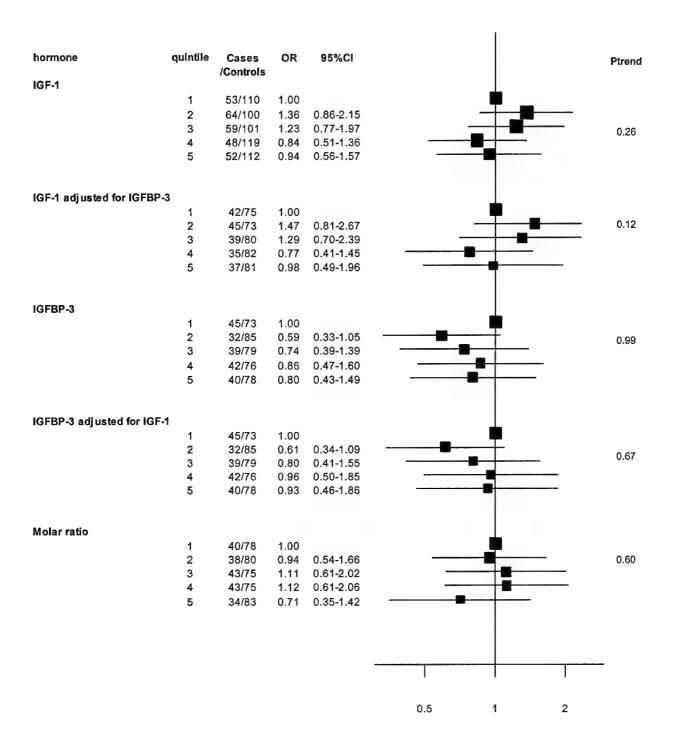


Figure 5. Relative risk of breast cancer among women older than 50 at diagnosis by quintiles of growth hormone levels

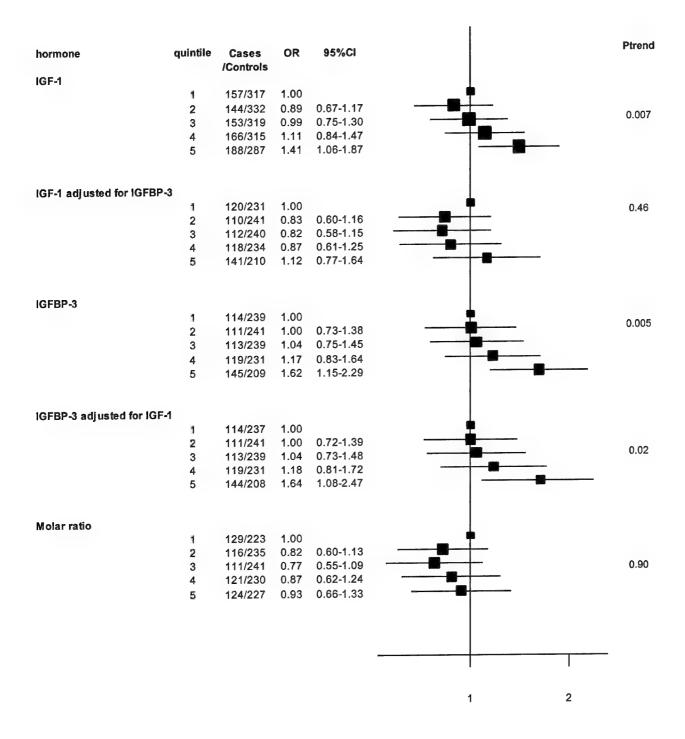


Figure 6. Relative risk of breast cancer among women younger than 60 at diagnosis by quintiles of growth hormone levels

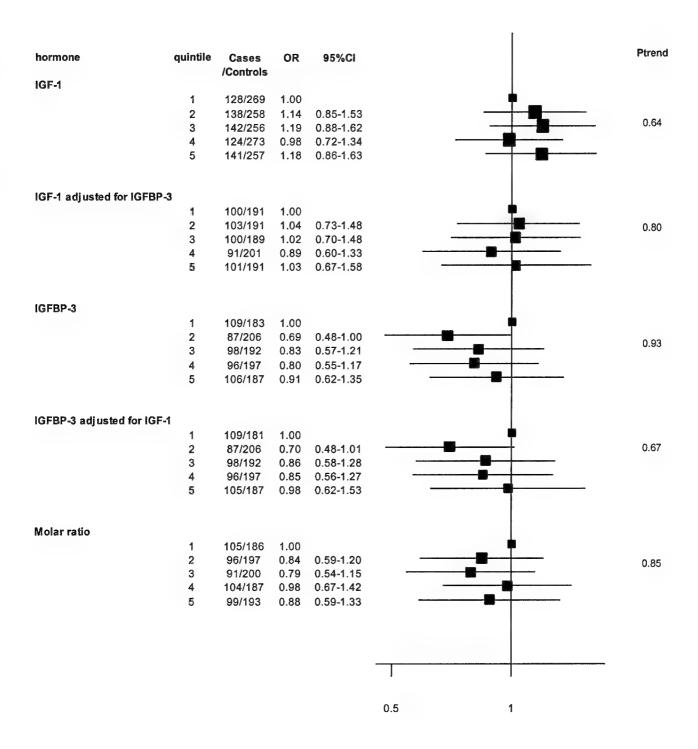


Figure 7. Relative risk of breast cancer among women older than 60 at diagnosis by quintiles of growth hormone levels

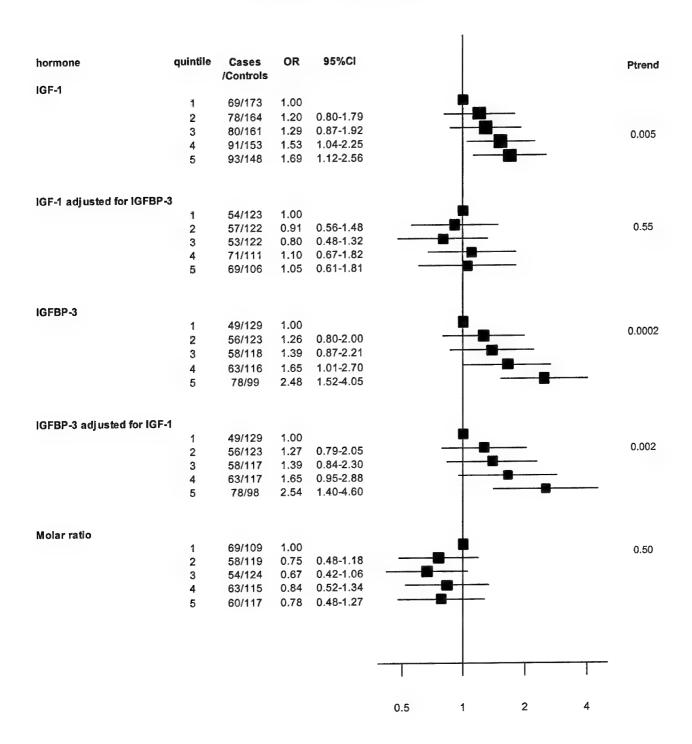


Table 1: Numbers of subjects genotyped for each of the 22 SNPs on 2342 subjects

SNP of the property of the second sec	Variables' names	N. Charles Street Street	N Missing	Frequency
11GHR_M28462_174AG	G11GHRSM28462AG	2297	45	1.92
16GHR_M28466_748AC	G16GHRSM28466AC	2312	30	1.28
24IGF1_X57025_3340AG	G24IGF1SX57025AG	2314	28	1.20
28IGFBP1_M74587_187AG	G28IGFBP1SM74587AG	2295	47	2.01
30IGFBP1_M74587_5110CT	G30IGFBP1SM74587CT	2317	25	1.07
311GFBP1_M74587_5179GA	G31IGFBP1SM74587GA	2322	20	0.85
331GFBP3_M35878_5709GC	G33IGFBP3SM35878GC	2289	53	2.26
36IGFBP3_M35878_8291CT	G36IGFBP3SM35878CT	2322	20	0.85
38IGFBP3_M35878_9156AG	G38IGFBP3SM35878AG	2327	15	0.64
39IGFBP3_M35878_10049AAG	G39IGFBP3SM35878AAG	2311	31	1.32
40SST_J00306_1399TC	G40SSTSJ00306TC	2302	40	1.71
46SSTR3_M96738_889GA	G46SSTR3SM96738GA	2298	44	1.88
53SSTR5_D16827_192CA	G53SSTR5SD16827CA	2318	24	1.02
56GHRELIN_AC008116_48106AG	G56GHRELINSAC008116AG	2303	39	1.67
57GHRELIN_AC008116_48002AC	G57GHRELINSAC008116AC	2325	17	0.73
58GHRELIN_AF269558_3857AT	G58GHRELINSAF269558AT	2312	30	1.28
59GHRELIN_AF296558_4060GT	G59GHRELINSAF296558GT	2278	64	2.73
66GHRHR_AC005155_58474AG	G66GHRHRSAC005155AG	2329	13	0.56
69GHRHR_AC005155_63007GA	G69GHRHRSAC005155GA	2317	25	1.07
72GHRHR_AC005155_64092GC	G72GHRHRSAC005155GC	2318	24	1.02
73GHRH_AL031659_91261TC	G73GHRHSAL031659TC	2315	27	1.15
75SSTR4_D16826_900GT	G75SSTR4SD16826GT	2304	38	1.62

Table 2: For each SNP, numbers of observations, means of IGF-I by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), p-values, R-square and R-square adjusted of different models with IGF-I as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGF-I

Gene	SIVE	NObs	Mean1 (Nobs)	Mean2 (Nobs)	Mean3 (Nobs)	Codo	Codominant model	lodel	Don	Dominant model 1 st allele	odel	Dom	Dominant model 2 nd allele		Average Excess
m, zakobu, sane a akeu, monte e resi						Pvalue	Rsq	q Adj	Pvalue	Rsq	Rsq Adj	Pvalue		Rsq	p-value
GHR	G11GHRSM28462AG	2296	240.9 (198)	240.5 (922)	239.3 (1176)	0.70	0.00007	0.000000.0	69.0	0.00007	0.000000	0.85	0.00002	0.00002 0.000000	0.67
	G16GHRSM28466AC	2311	239.8 (681)	240.4 (1093)	235.6 (537)	0.37	0.00034	0.000000	0.22	0.00063	0.000201	0.77	0.00004	0.000000	0.81
(GF1	G24IGF1SX57025AG	2313	239.2 (401)	238.7 (1114)	240.5 (798)	0.72	0.00006 0.000000	0.00000.0	0.62	0.00010	0.000000	96.0	0.00000	0.000000	0.36
[GFBP1	G28IGFBP1SM74587AG	2294	240.0 (320)	238.6 (1098)	239.7 (876)	96.0	0.00000 0.000000	0.000000	0.82	0.00002	0.000000	0.85	0.00002	0.000000.0	0.45
	G30IGFBP1SM74587CT	2316	239.0 (2134)	242.4 (174)	204.9 (8)	66.0	0.00000 0.000000	0.00000	0.21	0.00069	0.000254	0.77	0.00004	0.00004 0.000000	0.49
	G311GFBP1SM74587GA	2321	239.1 (262)	237.2 (1042)	241.2 (1017)	0.40	0.00030	0.000000	0.26	0.00054	0.000113	66.0	0.00000	0.000000	0.20
(GFBP3	G331GFBP3SM35878GC	2288	246.0 (99)	241.3 (762)	236.9 (1427)	0.11	0.00112	0.000687	0.13	0.00098	0.000546	0.34	0.00040	0.000000	0.05
	G36IGFBP3SM35878CT	2321	238.7 (2282) 279.2 (39)	279.2 (39)		0.001	0.00458 0.004151	0.004151		0.00000	0.000000	0.001	0.00458	0.004151	<0.01
	G38IGFBP3SM35878AG	2326	239.0 (1506)	239.4 (734)	240.6 (86)	0.85	0.00002	0.000000.0	0.87	0.00001	0.000000	88.0	0.00001	0.000000	0.42
	G39IGFBP3SM35878AAG	2310	240.1 (1693) 236.1 (577)	236.1 (577)	234.3 (40)	0.25	0.00057	0.000140	0.70	0.00007	0.000000	0.25	0.00058	0.000143	0.88
SST	G40SSTSJ00306TC	2301	240.5 (1859)	232.8 (418)	246.7 (24)	0.15	0.00092	0.000488	0.63	0.00010	0.000000.0	0.09	0.00126	0.000825	90.0
SSTR3	G46SSTR3SM96738GA	2297	238.5 (1455)	240.3 (729)	243.8 (113)	0.42	0.00029	0.000000	0.52	0.00018	0.0000000	0.48	0.00021	0.000000	0.23
SSTR5	G53SSTR5SD16827CA	2317	240.0 (2057)	233.7 (255)	187.1 (5)	0.11	0.00110	0.000667	0.13	0.00099	0.000559	0.16	0.00087	0.000439	0.05
GHRELIN	G56GHRELINSAC008116AG	2302	239.8 (801)	236.8 (1111)	243.2 (390)	0.71	9000000	0.000000.0	0.23	0.00062	0.000187	69:0	0.00007	0.000000	0.35
	G57GHRELINSAC008116AC	2324	240.8 (1070)	240.8 (1070) 237.2 (1012)	239.8 (242)	0.51	0.00019	0.00000 0.000000	0.89	0.00001	0.000000	0.34	0.00040	0.000000	0.73
	G58GHRELINSAF269558AT	2311	239.1 (2027)	238.1 (273)	247.6 (11)	96.0	0.00000	0.000000	0.71	0.00006	0.000000	0.90	0.00001	0.000000	0.52
	G59GHRELINSAF296558GT	2277	242.4 (645)	237.4 (1080)	238.9 (552)	0.39	0.00032	0.000000	0.92	0.00001	0.000000	0.20	0.00071	0.000273	0.81
GHRHR	G66GHRHRSAC005155AG	2328	240.5 (1252)	238.8 (916)	230.9 (160)	0.19	0.00073	0.000305	0.16	0.00085	0.000423	0.36	0.00036	0.000000	0.91
	G69GHRHRSAC005155GA	2316	239.2 (1853)	239.6 (439)	222.3 (24)	0.72	0.00006	0.000000	0.28	0.00050	0.000069	0.91	0.00001	0.000000	0.63
	G72GHRHRSAC005155GC	2317	239.8 (1121)	239.3 (985)	235.4 (211)	0.54	0.00016	0.000000	0.46	0.00024	0.00000	0.71	0.00006	0.000000	0.74
GHRH	G73GHRHSAL031659TC	2314	238.8 (2218)	247.5 (96)		0.28	0.00051	0.000075		0.00000	0.000000	0.28	0.00051	0.000075	0.11
SSTR4	G75SSTR4SD16826GT	2303	240.4 (359)	241.1 (1094)	236.0 (850)	0.22	0.00065	0.00065 0.000213	0.14	0.00097	0.00097 0.000531	0.73	0.00005	0.00005 0.000000	0.90

Table 3: For each SNP, numbers of observations, means of IGFBP3 by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), pvalues, R-square and R-square adjusted of different models with IGFBP3 as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGFBP3

	ans	NOF	Moont	Caronia of	Moone	and the second second	Commence of the second	Salay Services provided	The state of the s		odol	Des			A
		3	(Nobs)	(Nobs)	(Nobs)				3	1st allele			2 nd allele		Excess
						Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq	p-value
GHR	G11GHRSM28462AG	2292	2939 (196)	3003 (920)	2956 (1176)	0.54	0.00017	0.000000	0.23	0.00063	0.000192	0.47	0.00023	0.000000	0.73
	G16GHRSM28466AC	2308	2953 (680)	2988 (1092)	2964 (536)	0.73	0.00005	0.000000	0.75	0.00004	0.000000	0.40	0.00031	0.000000	0.35
IGF1	G24IGF1SX57025AG	2309	2966 (399)	2956 (1113)	3005 (797)	0.25	0.00058	0.000142	0.14	0.00096	0.00096 0.000524	0.79	0.00003	0.000000.0	0.08
(GFBP1	G28IGFBP1SM74587AG	2290	2949 (318)	2991 (1096)	2965 (876)	76.0	0.00000	0.00000 0.000000	0.57	0.00014	0.00014 0.000000	0.47	0.00023	0.000000.0	0.51
	G30IGFBP1SM74587CT	2312	2967 (2130)	3029 (174)	3268 (8)	0.14	9600000	0.000530	0.24	0.00061	0.00061 0.000176	0.18	0.00077	0.000334	90.0
	G31IGFBP1SM74587GA	2317	2941 (260)	2977 (1041)	2978 (1016)	95.0	0.00015	0.000000	0.78	0.00003	0.000000.0	0.43	0.00027	0.000000	0.30
(GFBP3	G33IGFBP3SM35878GC	2284	2741 (99)	2928 (760)	3014 (1425)	<.0001	0.00758	0.00758 0.007146	0.0004	0.00545	0.00545 0.005010	0.001	0.00492	0.004487	<0.001
	G36IGFBP3SM35878CT	2317	(8/22) //62	2777 (39)		80.0	0.00134	0.000905		0.00000		80.0	0.00134	0.000905	0.04
	G38IGFBP3SM35878AG	2322	2979 (1505)	2954 (731)	3020 (86)	0.78	0.00003	0.000000	0.53	0.00017	0.000000	0.57	0.00014	0.000000.0	0.61
	G39IGFBP3SM35878AAG	2306	2962 (1691)	3002 (575)	3044 (40)	0.18	8/00000	0.000344	0.52	0.00018	0.000000	0.20	0.00072	0.000285	0.09
SST	G40SSTSJ00306TC	2297	2967 (1856)	2998 (417)	2880 (24)	0.65	6000000	0.000000	0.52	0.00018	0.000000.0	0.51	6100000	0.000000	0.32
SSTR3	G46SSTR3SM96738GA	2293	2979 (1453)	2966 (728)	2959 (112)	0.65	0.00009	0.00000 0.000000	0.83	0.00002	0.000000	0.65	6000000	0.000000.0	89.0
SSTR5	G53SSTR5SD16827CA	2313	2974 (2053)	2977 (255)	2737 (5)	0.88	0.00001	0.000000	0.45	0.00025	0.000000	76.0	0.00000	0.000000.0	0.55
GHRELIN	G56GHRELINSAC008116AG	2298	2998 (800)	2962 (1109)	2976 (389)	0.46	0.00024	0.00024 0.000000	86.0	0.00000	0.00000 0.000000	0.29	0.00049	0.000053	0.73
	G57GHRELINSAC008116AC	2320	2975 (1067)	2952 (1010)	3064 (243)	0.35	0.00038	0.000000	0.04	0.00188	0.001452	0.97	0.00000	0.000000.0	0.18
	G58GHRELINSAF269558AT	2307	2968 (2024)	3002 (272)	3011 (11)	0.44	0.00026	0.00026 0.000000	0.85	0.00002	0.000000	0.44	0.00026	0.000000	0.23
	G59GHRELINSAF296558GT	2273	3021 (645)	2980 (1078)	2916 (550)	0.01	0.00287	0.00287 0.002426	0.02	0.00235	0.001910	90.0	0.00159	0.001152	0.02
GHRHR	G66GHRHRSAC005155AG	2324	2970 (1250)	2958 (916)	3078 (158)	0.34	0.00039	0.000039 0.0000000	0.05	0.00164	0.001214	0.85	0.00002	0.000000.0	0.18
	G69GHRHRSAC005155GA	2312	2970 (1850)	2989 (438)	2912 (24)	0.78	0.00003	0.000000	0.67	0.00008	0.000000	0.68	0.00007	0.000000	0.41
	G72GHRHRSAC005155GC	2313	2964 (1120)	2966 (984)	3052 (209)	0.22	0.00064	0.000208	60.0	0.00127	0.000833	0.55	0.00015	0.000000.0	0.11
GHRH	G73GHRHSAL031659TC	2310	2970 (2214)	3006 (96)		0.62	0.00010	0.00010 0.000000		0.00000		0.62	0.00010	0.000000.0	0.31
SSTR4	G75SSTR4SD16826GT	2299	2978 (358)	2978 (1092)	2965 (849)	0.71	0.00006	0.00000 0.000000	29.0	0.00008	0.000000	68.0	0.00001	0.000000	99.0

Table 4: Number of SNPs per gene, R-square adjusted of full rank haplotype models and results of stepwise regression models

GHR 2 0.000 IGFI 1 0.000 IGFBP1 3 0.000 IGFBP3 4 0.000 SSTR 1 0.000 SSTRS 1 0.000 GHRELIN 4 0.000 GHRHR 3 0.000 GHRH 1 0.000	Gene Number of SNPs R ² adj of full ranl	of full rank ("maximum")	Result from step	Result from stepwise regression:
2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	haplotype model (Rsq)	odel (Rsq)	Nr of SNP loci showing effects / n	Nr of SNP loci showing effects / model p-value / model R ² adj (Rsq)
2 PP1 3 SP3 4 1 1 SS 1 ELIN 4 HR 3 HR 3	IGF-1	IGFBP-3	IGF-1	IGFBP-3
8P1 3 8P3 4 1 1 83 1		0.0004 (.002)	1	/
3P1 3 4 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	0.0000 (.0001)	0.0005 (.001)	/	/
3P3 4	0.0000 (.002)	0.0004 (.002)	1	/
R3 1	0.003 (.006)	0.007 (.0103)	$1/p=.001/R^2=(.0005).004$	$1 / p=.001 / R^2=(.008).007$
1 4 6 1	0.0008 (.001)	0.0000 (.0005)	1	/
3 4 4	0.0000 (.0003)	0.0000 (.0001)	1	/
4 6 1	0.0008 (.002)	0.0000 (.0001)	1	/
R 3	0.0000 (.002)	0.0035 (.007)	$2 / p=.02 / R^2=(.008).004$	$2 / p=.01 / R^2=(.005).003$
	0.0000 (.002)	0.0000 (.002)	1	/
	0.0001 (.0005)	0.0000 (.0001)	/	1
SSTR4 1 0.00	0.0005 (.001)	0.0000 (.0001)		1

Table 5: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHR	G11	622	1507	2286	•	•	•	0.6952		0.8366	٠	0.2887
	G111	19	138	199		•	•	•	240.613	•	2940.60	·
	G112	322	601	923	1.207	0.869	1.677	0.2620	240.995	٠	3001.12	
	G113	396	768	1164	1.158	0.837	1.603	0.3753	239.023		2957.27	•
GHR	G16	774	1517	1622	•			0.9917		0.4771		0.6211
	G161	219	454	673	•	•	٠	•	239.862	•	2953.04	·
	G162	387	708	1095	1.139	0.925	1.402	0.2202	240.740	٠	2986.75	,
	G163	168	355	523	0.982	0.766	1.259	0.8877	235.851	٠	2976.15	·
IGF1	G24	774	1521	2295	•	•	٠	0.2417	٠	0.5469	•	0.2918
	G241	131	271	402	•	·	•	•	238.896	٠	2982.14	•
	G242	364	749	1113	666'0	0.783	1.273	0.9913	238.215		2955.57	·
	G243	279	501	780	1.133	0.879	1.460	0.3357	242.073	•	3007.18	·
IGFBP1	G28	770	1497	2267	٠	•	•	0.7454		0.8628	•	0.4479
	G281	114	208	322	•	•	٠	-	240.002	٠	2946.05	,
	G282	353	734	1087	0.871	0.671	1.131	0.2992	238.277	•	2993.69	•
	G283	303	555	858	0.981	0.751	1.281	0.8865	240.044	٠	2961.21	٠
IGFBP1	G30	9//	1524	2300	•	•	•	0.7178	٠	0.4384	•	0.2107
	G301	712	1407	2119	•	•	•	•	239.301		2967.49	•
	G302	62	111	173	1.110	0.799	1.543	0.5330	240.550	•	3041.25	٠
	G303	2	9	8	0.667	0.135	3.303	0.6197	204.883	٠	3267.95	•
IGFBP1	G31	780	1533	2313	•	•	•	0.7641	٠	0.3612		0.6120
	G311	68	175	264	•	•	•	•	239.072	•	2934.10	•
	G312	345	693	1038	0.977	0.733	1.303	0.8739	236.931	•	2979.98	•
	G313	346	599	1011	1.019	0.762	1.362	0.8988	241.774	g	2980.28	•

Gene	Variable	cases	controls	и	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
IGFBP3	G33	191	1489	2256			•	0.9793	•	0.2275	•	<.0001
	G331	38	59	76	•	٠	•	•	246.473	•	2708.65	•
	G332	247	206	753	0.763	0.493	1.183	0.2270	241.850	•	2924.81	•
	G333	482	924	1406	0.824	0.540	1.258	0.3702	236.949		3022.11	٠
IGFBP3	G36	9//	1529	2305	•		•	0.3330	•	0.0019	•	0.0584
	G361	992	1501	2267	*	٠	•	•	238.807	•	2977.93	•
	G362	10	28	38	0.700	0.340	1.442	0.3330	277.659	•	2759.58	•
	G363	•	٠	٠	•	٠	٠	•	٠	•	•	٠
IGFBP3	G38	782	1540	2322	•	•	•	0.1892	•	0.9739	•	0.7130
	G381	521	086	1501	•	•	•	•	239.216	•	2980.09	٠
	G382	234	501	735	0.880	0.727	1.065	0.1900	239.219	•	2957.79	•
	G383	27	59	98	0.871	0.549	1.383	0.5588	241.154	•	3006.51	•
IGFBP3	G39	778	1520	2298	•	•	•	0.5523	٠	0.4213	•	0.3914
	G391	563	1115	1678	•	•	•	•	240.555	٠	2964.44	·
	G392	201	379	580	1.059	0.864	1.299	0.5787	235.856	•	3009.31	
	G393	14	26	40	1.092	0.569	2.095	0.7916	235.352	٠	3014.71	
SST	G40	775	1510	2285	•	•	•	0.0454	•	0.1040	•	0.4577
	G401	809	1241	1849	•	•	•	•	240.855	٠	2965.64	
	G402	158	255	413	1.251	1.001	1.562	0.0487	232.159	•	3006.97	
	G403	6	14	23	1.311	0.565	3.043	0.5283	246.274	•	2876.80	
SSTR3	G46	772	1501	2273	•	•	•	0.8182	•	0.6986	•	0.9457
	G461	491	945	1436		•	•	•	238.638	•	2976.59	
	G462	243	483	726	0.970	0.803	1.172	0.7527	240.654	٠	2965.80	
	G463	38	73	111	966'0	0.662	1.498	0.9829	243.924	•	2974.45	

Gene	Variable	cases	controls	g	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
SSTR5	G53	692	1518	2287	٠	•	•	0.3062	٠	0.1509		0.7075
	G531	929	1358	2034	٠	•	•	•	239.961	٠	2974.45	•
	G532	92	156	248	1.192	0.906	1.568	0.2084	233.738	٠	2991.32	•
	G533	-	4	5	0.501	0.056	4.477	0.5364	187.100	٠	2736.98	•
GHRELIN	G56	9//	1512	2288	•		•	0.7585	•	0.2896		0.3989
	G561	272	523	795	٠	٠	•	•	240.740	•	3006.25	,
	G562	376	729	1105	0.994	0.821	1.203	0.9497	236.573	·	2965.22	•
	G563	128	260	388	0.956	0.739	1.238	0.7332	242.827	-	2961.63	•
GHRELIN	G57	180	1535	2315	•	•	•	0.6534	·	0.6764		0.0797
	G571	361	969	1057	٠	•	•	•	240.200		2972.50	•
	G572	340	929	1016	0.974	0.810	1.172	0.7830	237.632		2955.66	•
	G573	79	163	242	0.937	0.694	1.265	0.6693	241.301	·	3069.31	
GHRELIN	G58	773	1518	1622	•	·	•	0.0270	٠	0.8780	•	0.6936
	G581	662	1347	2009	•	•	•	٠	239.290	٠	2969.32	•
	G582	106	165	271	1.314	1.011	1.708	0.0408	237.550		3007.82	٠
	G583	5	9	11	1.711	0.522	5.611	0.3753	247.643		3011.32	
GHRELIN	G59	652	1469	2228	•	*	•	0.4480		0.3383		0.0190
	G591	217	419	636	•	•	•	•	243.175	•	3024.12	•
	G592	370	989	1056	1.037	0.844	1.274	0.7309	237.800	٠	2985.13	•
	G593	172	364	536	0.906	0.712	1.153	0.4227	238.166	•	2909.03	•
GHRHR	995	782	1541	2323	•			0.2385	·	0.1942	•	0.1629
	G661	433	822	1255	•	•	•	•	241.186	٠	2975.90	•
	G662	302	809	910	0.943	0.788	1.128	0.5178	238.077		2954.66	٠
	G663	47	111	158	0.808	0.565	1.154	0.2403	230.077	٠	3071.33	٠

Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRHR	695	775	1525	2300	•	•	•	0.2928	•	0.6572		0.9420
	G691	809	1220	1828	•	٠	٠	٠	239.143	٠	2971.99	•
	G692	157	292	449	1.078	0.870	1.336	0.4917	240.066	•	2981.98	•
	G693	10	13	23	1.559	0.683	3.559	0.2916	225.122	٠	2941.37	•
GHRHR	G72	775	1526	2301	•	•	•	0.0705	٠	0.6981	•	0.2317
	G721	392	723	1115		٠	•	•	240.186	٠	2969.26	•
	G722	322	651	973	0.910	0.758	1.092	0.3091	239.523	•	2960.21	•
	G723	61	152	213	0.753	0.549	1.034	0.0792	235.330	٠	3050.88	•
GHRH	G73	9//	1522	2298	•	•	•	0.5009	٠	0.2513	•	0.5514
	G731	741	1462	2203	•	•	٠	•	238.711	•	2968.93	٠
	G732	35	09	95	1.160	0.753	1.787	0.5009	247.932	•	3012.96	•
	G733	٠	•		*	•	•	٠	•	٠	٠	•
SSTR4	G75	765	1501	2266	•	•	٠	0.7021	•	0.3180	•	0.9147
	G751	112	242	354	•	٠	•	•	240.398	•	2987.89	•
	G752	377	710	1087	1.172	0.905	1.517	0.2283	241.032	•	2972.68	٠
	G753	276	549	825	1.105	0.841	1.451	0.4742	235.834	•	2969.07	•

Dominant model 1st allele

Table 6: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele and heterozygotes, homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

CHR G11 735 CMST Free Activity Free Activity <th></th>													
G11 779 1507 2286 0.9282 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5825 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5915 0.5916	Gene	Variable	cases	controls	e	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
Cill 396 768 1164	GHR	G11	179	1507	2286	•	•	•	0.9282		0.5525	·	0.2580
G116 383 739 1122 1008 0.8445 1203 0.9282 240.927 299.04.9 G16 774 1517 2291 0.3658 0.235.81 299.04.9 G161 168 355 523 235.851 297.13 G162 660 1162 1768 235.851 297.91 PPI G24 774 1152 1768 235.851 297.91 PPI G24 774 1521 226 240.40 297.91 PPI G24 775 189		G111	396	292	1164	•	٠	٠	•	239.023	•	2957.27	•
G16 774 1517 2291 0.3628 0.2324 <th< th=""><th></th><th>G112</th><th>383</th><th>739</th><th>1122</th><th>1.008</th><th>0.845</th><th>1.203</th><th>0.9282</th><th>240.927</th><th>•</th><th>2990.49</th><th>٠</th></th<>		G112	383	739	1122	1.008	0.845	1.203	0.9282	240.927	•	2990.49	٠
G161 168 355 523 235,851 2976,15 G162 606 1162 1768 11,103 0.893 1,364 0.3628 240,406 2976,15 R1 G24 774 1521 295	GHR	G16	774	1517	2291	•	•	•	0.3628	٠	0.2324	·	0.9495
G162 606 1162 1768 1.103 0.893 1.364 0.3628 240.406 297.302 G24 774 1521 2295 0.1714 0.2766 PP G241 279 361 780 0.1714 0.2763 297.30 PP G242 495 1020 1515 0.882 0.737 1.056 0.1714 238.36 296.20 PP G282 470 1497 2267 0.1741 238.36 296.20 PP G381 303 555 858 8.8		G161	168	355	523	•	•	•	•	235.851	٠	2976.15	
Q24 774 1521 2256 0.1714 0.2766 P1 G241 780 152 780 242.073 242.073 3007.18 P1 G242 495 1020 1515 0.882 0.737 1.056 0.1714 238.396 296.20 P1 G28 770 1497 2267 0.737 0.743 22.00 296.21 P2 G28 30 555 858 0.767 1.097 0.2432 23.837 296.21 P3 452 1409 0.917 0.767 1.097 0.3432 23.837 296.21 P3 430 152 200		G162	909	1162	1768	1.103	0.893	1.364	0.3628	240.406	٠	2973.92	•
G241 279 501 780 242,073 242,073 242,073 242,073 242,073 242,073 242,073 242,073	IGF1	G24	774	1521	2295	•	•	٠	0.1714	•	0.2766	•	0.1524
G281 495 1020 1515 0.882 0.737 1.056 0.1714 238.396 9. 2962.60 G281 770 1497 2267 <		G241	279	501	780	•	•	•	•	242.073	•	3007.18	٠
G281 770 1497 2267 0.3432 0.6802 G281 303 555 858 240.044 2561.21 G282 467 942 1409 0.917 0.767 1.097 0.3432 238.671 2961.21 G302 776 1524 230 0.6197 292.83 G301 72 1524 230 0.30 74.29 0.6197 229.36 297.30 G311 780 153 2313 <th< th=""><th></th><th>G242</th><th>495</th><th>1020</th><th>1515</th><th>0.882</th><th>0.737</th><th>1.056</th><th>0.1714</th><th>238.396</th><th>•</th><th>2962.60</th><th></th></th<>		G242	495	1020	1515	0.882	0.737	1.056	0.1714	238.396	•	2962.60	
G281 303 555 858 240,044 240,044 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,041 240,043 240,041 240,043 .	IGFBP1	G28	770	1497	2267	•	•	•	0.3432	٠	0.6802		0.4825
G282 467 942 1409 0.917 0.767 1.097 0.3432 238.671 0.2048 292.83 G301 22 1524 230 23 23 20.6197 204.883 23.67.95 G301 22 1.500 0.303 7.429 0.6197 239.396 297.308 G312 78 1.53 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313 2313		G281	303	555	828	٠	•	٠	•	240.044	•	2961.21	•
G301 776 1524 2300 . . . 0.6197 . 0.02048 . G301 2 8 </th <th></th> <th>G282</th> <th>467</th> <th>942</th> <th>1409</th> <th>0.917</th> <th>0.767</th> <th>1.097</th> <th>0.3432</th> <th>238.671</th> <th>•</th> <th>2982.83</th> <th></th>		G282	467	942	1409	0.917	0.767	1.097	0.3432	238.671	•	2982.83	
G301 2 6 8 1.500 0.303 7.429 0.6197 294.883 3267.95 G302 774 1518 2292 1.500 0.303 7.429 0.6197 239.396 2973.08 G31 78 153 2313 2313 2313 2313 2313 2313 2313 2313 2314 8.6 1011 8.60 1.148 0.6754 237.365 2980.28 G33 767 1489 2256 0.6435 236.949 2970.71 G332 285 850 0.958 0.798 1.149 0.6435 242.378 2900.06 Annual Mark <th>IGFBP1</th> <th>G30</th> <th>176</th> <th>1524</th> <th>2300</th> <th>•</th> <th>•</th> <th>•</th> <th>0.6197</th> <th>٠</th> <th>0.2048</th> <th>٠</th> <th>0.2399</th>	IGFBP1	G30	176	1524	2300	•	•	•	0.6197	٠	0.2048	٠	0.2399
G312 774 1518 2292 1.500 0.303 7.429 0.6197 239.396 2973.08 G31 780 1533 2313 2313 2313 2313 2313 2313 2313 2314 767 1011 7617 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 76171 <td< th=""><th></th><th>G301</th><th>2</th><th>9</th><th>8</th><th>٠</th><th>٠</th><th>•</th><th>•</th><th>204.883</th><th>•</th><th>3267.95</th><th>٠</th></td<>		G301	2	9	8	٠	٠	•	•	204.883	•	3267.95	٠
G311 780 1533 2313 <		G302	774	1518	2292	1.500	0.303	7.429	0.6197	239.396	•	2973.08	•
G311 346 665 1011 <th< th=""><th>IGFBP1</th><th>G31</th><th>780</th><th>1533</th><th></th><th>•</th><th>•</th><th>•</th><th>0.6754</th><th>•</th><th>0.1711</th><th>•</th><th>0.7475</th></th<>	IGFBP1	G31	780	1533		•	•	•	0.6754	•	0.1711	•	0.7475
G312 434 868 1302 0.963 0.808 1.148 0.6754 237.365 9 2970.71 G33 767 1489 2256 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 7 8 7 8 7 8 7 8 9 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 <t< th=""><th></th><th>G311</th><th>346</th><th>999</th><th>1011</th><th>•</th><th>٠</th><th>٠</th><th>•</th><th>241.774</th><th>•</th><th>2980.28</th><th>•</th></t<>		G311	346	999	1011	•	٠	٠	•	241.774	•	2980.28	•
G33 767 1489 2256 . . . 0.6435 . 0.1036 . G331 482 924 1406 . . . 236.949 . 3022.11 G332 285 850 0.958 0.798 1.149 0.6435 242.378 . 2900.06 A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		G312	434	898	1302	0.963	0.808	1.148	0.6754	237.365	•	2970.71	•
482 924 1406 236.949 . . 285 565 850 0.958 0.798 1.149 0.6435 242.378 .	IGFBP3	G33	167	1489	2256	•	٠	•	0.6435		0.1036	•	<.0001
285 565 850 0.958 0.798 1.149 0.6435 242.378		G331	482	924	1406	•	•	•	•	236.949	•	3022.11	٠
		G332	285	265	850	0.958	0.798		0.6435	242.378	•	2900.06	·

Dominant model 1st allele

Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
IGFBP3	G38	782	1540	2322	•	•		0.6735		0.8182	•	0.6642
	G381	27	59	98	•	•		•	241.154	·	3006.51	•
	G382	755	1481	2236	1.104	0.698	1.745	0.6735	239.217	•	2972.78	٠
IGFBP3	G39	178	1520	2298	•	•	•	0.8210	•	0.7435	•	0.7287
	G391	14	26	40	٠	•	•	•	235.352	٠	3014.71	•
	G392	764	1494	2258	0.928	0.485	1.776	0.8210	239.349		2975.93	•
SST	G40	775	1510	2285	•	•	•	0.6075		0.6630	•	0.5165
	G401	6	14	23	•	•	•	٠	246.274	•	2876.80	٠
	G402	992	1496	2262	0.803	0.347	1.858	0.6075	239.265	•	2973.18	٠
SSTR3	G46	772	1051	2273	٠	•	•	0.9727	•	0.5358	•	0.9830
	G461	38	73	111	•	•	•	•	243.924	•	2974.45	•
	G462	734	1428	2162	0.993	0.664	1.485	0.9727	239.315	٠	2972.97	•
SSTR5	G53	692	1518	2287	•	•	•	0.5364	•	0.1277	•	0.4513
	G531	1	4	5		٠	٠	•	187.100	٠	2736.98	*
	G532	768	1514	2282	1.995	0.223	17.821	0.5364	239.283		2976.29	
GHRELIN	G56	176	1512	2288	•	•	•	0.7266		0.2914	·	0.5983
	G561	128	260	388	٠	* ;	*	•	242.827	٠	2961.63	-
	G562	648	1252	1900	1.042	0.827	1.312	0.7266	238.316	•	2982.39	•
GHRELIN	G57	780	1535	2315	•	•	•	0.7192	٠	0.6519	•	0.0290
	G571	79	163	242	•	•	•	•	241.301	•	3069.31	
	G572	701	1372	2073	1.054	0.792	1.402	0.7192	238.943	٠	2964.25	·
CHRELIN	G58	773	1518	2291			٠	0.3988	٠	0.7114	•	0.8611
	G581	5	9	11	•		•	٠	247.643	•	3011.32	
	G582	892	1512	2280	0.600	0.183	1.966	0.3988	239.083	•	2973.88	

Dominant model 1st allele

Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRELIN	G59	759	1469	2228	•	•	•	0.2408	•	0.6613	•	9600.0
	G591	172	364	536	٠	•	•	•	238.166	٠	2909.03	•
	G592	587	1105	1692	1.129	0.922	1.382	0.2408	239.820	•	2999.77	•
GHRHR	99D	782	1541	2323		•	•	0.2884	•	0.1205	٠	0.0758
	G661	47	111	158	٠	•	٠	•	230.077	٠	3071.33	•
	G662	735	1430	2165	1.208	0.852	1.712	0.2884	239.880	•	2966.97	•
GHRHR	69D	775	1525	2300		•	•	0.3057	٠	0.3750	•	0.8263
	G691	10	13	23	•	•	٠	٠	225.122	٠	2941.37	•
	G692	765	1512	7772	0.650	0.285	1.482	0.3057	239.325	·	2973.96	•
GHRHR	G72	775	1526	2301	•	•	•	0.1222	•	0.4096	•	0.0920
	G721	19	152	213	•	•	•	•	235.330	•	3050.88	
	G722	714	1374	2088	1.273	0.937	1.728	0.1222	239.877	•	2965.05	•
SSTR4	G75	292	1501	5266	•	٠	•	0.7927	•	0.1316	•	0.8127
	G751	276	549	825	•	•	•	•	235.834	·	2969.07	•
	G752	489	952	1441	1.025	0.854	1.230	0.7927	240.876	٠	2976.42	

Dominant model 2nd allele

Table 7: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele, heterozygotes and homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

6				- 1			To comm.	CICAL S COSES				
Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHR	G11	622	1507	5286	·	•	•	0.2990	•	0.8995	•	0.4911
	G111	19	138	199	٠	•	•		240.613	٠	2940.60	
	G112	718	1369	2087	1.181	0.863	1.615	0.2990	239.896	٠	2976.65	٠
GHR	G16	774	1517	2291	·	٠	•	0.4107	•	0.8412	•	0.3501
	G161	219	454	673	•	•	•		239.862		2953.04	
	G162	555	1063	1618	1.085	0.893	1.318	0.4107	239.158	•	2983.32	•
IGF1	G24	<i>774</i>	1521	2295	٠	٠	•	0.6586	•	0.8291		0.8917
	G241	131	271	402	•	٠	•		238.896	·	2982.14	•
	G242	643	1250	1893	1.053	0.838	1.323	0.6586	239.805		2976.84	٠
IGFBP1	G28	170	1497	2267	٠	٠	•	0.4991	•	0.8378	•	0.4367
	G281	114	208	322	·	•	•	٠	240.002	٠	2946.05	•
	G282	959	1289	1945	0.919	0.718	1.175	0.4991	239.056	•	2979.35	•
IGFBP1	G30	9//	1524	2300	•	•	•	0.6188	•	1956.0		0.1268
	G301	712	1407	2119	•	٠	•	•	239.301	•	2967.49	٠
	G302	64	117	181	1.085	0.787	1.497	0.6188	238.974	•	3051.27	
IGFBP1	G31	780	1533	2313	•	٠	٠	0.9814	•	8096.0	٠	0.3217
	G311	89	175	264	•	•	•	•	239.072	٠	2934.10	•
	G312	169	1358	2049	0.997	0.758	1.311	0.9814	239.319	٠	2980.12	•
IGFBP3	G33	191	1489	2256	٠	٠	•	0.3068	•	0.3265	•	0.0001
	G331	38	59	97	٠	•	•	٠	246.473	•	2708.65	·
	G332	729	1430	2159	0.804	0.529	1.222	0.3068	238.658	•	2988.18	•

Dominant model 2nd allele

IGFBP3 (G36 G361			1				homonori	шсап			
	G361	9//	1529	2305	٠	•	•	0.3330	٠	0.0019	٠	0.0584
		992	1501	2267		•	•	•	238.807	•	2977.93	•
	G362	10	28	38	0.700	0.340	1.442	0.3330	277.659	•	2759.58	•
	G38	782	1540	2322	•	•	•	0.1686	٠	0.9507	•	0.5769
	G381	521	086	1501	٠	•	٠	•	239.216	•	2980.09	٠
	G382	261	260	821	0.879	0.732	1.056	0.1686	239.422	•	2962.92	
IGFBP3 (G39	778	1520	2298	•	•	•	0.5522	·	0.1887	·	0.1710
	G391	563	1115	1678	•	•	•	•	240.555	•	2964.44	·
	G392	215	405	620	1.062	128.0	1.294	0.5522	235.823	•	3009.66	
SST	G40	277	1510	2285	•	•	•	0.0421	٠	0.0516		0.3626
_	G401	809	1241	1849	•	•	•		240.855	,	2965.64	·
	G402	167	269	436	1.254	1.008	1.559	0.0421	232.903	·	3000.07	•
SSTR3	G46	772	1501	2273		•	٠	0.7695	•	0.4618	٠	0.7546
	G461	491	945	1436	•	•	٠	•	238.638	•	2976.59	•
	G462	281	556	837	0.973	0.811	1.167	0.7695	241.088		2966.93	
SSTR5	G53	691	1518	2287	•		•	0.2500	•	0.1614	•	0.8024
	G531	9/9	1358	2034	•	•	•	•	239.961		2974.45	
	G532	93	160	253	1.173	0.894	1.538	0.2500	232.816	•	2986.29	
GHRELIN	G56	9//	1512	2288		·	•	0.8648	•	0.4501	•	0.1760
	G561	272	523	795	•	•	•	•	240.740	·	3006.25	
	G562	504	686	1493	0.984	0.821	1.181	0.8648	238.196	•	2964.29	
GHRELIN	G57	780	1535	2315	•	•	٠	0.7087	٠	0.5611	•	0.8634
	G571	361	969	1057		•	•	•	240.200	٠	2972.50	
	G572	419	839	1258	196.0	0.811	1.153	0.7087	238.336	•	2977.60	

Dominant model 2nd allele

Gene	Variable	cases	controls	п	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRELIN	G58	773	1518	2291	٠		•	0.0301		0.7821		0.3923
	G581	662	1347	2009			•	•	239.290	٠	2969.32	•
	G582	111	171	282	1.329	1.028	1.718	0.0301	237.943		3007.95	
GHRELIN	G59	652	1469	2228	•	•	•	0.9215	•	0.1416	•	0.0514
	G591	217	419	636	•	٠	•	٠	243.175	٠	3024.12	
	G592	542	1050	1592	0.660	0.817	1.201	0.9215	237.923		2959.52	
GHRHR	995	782	1541	2323	•	•	•	0.3530	٠	0.1785	•	0.8858
	G661	433	823	1255	•	•	•	•	241.186	٠	2975.90	
	G662	349	719	1068	0.922	7777	1.094	0.3530	236.891	•	2971.67	•
GHRHR	69D	<i>SLL</i>	1525	2300	•	•	•	0.3786	•	0.9609	•	0.8272
	G691	809	1220	1828	٠	•		•	239.143	٠	2971.99	
	G692	167	305	472	1.099	0.891	1.355	0.3786	239.336	,	2980.00	•
GHRHR	G72	277	1526	2301	•	•		0.1422	•	0.6575	,	0.8091
	G721	392	723	1115	•	٠	•	•	240.186	٠	2969.26	
	G722	383	803	1186	0.879	0.739	1.044	0.1422	238.768	•	2976.36	
GHRH	G73	9//	1522	2298	•	•	·	0.5009	•	0.2513	٠	0.5514
	G731	741	1462	2203	•	٠	٠	•	238.711	٠	2968.93	
	G732	35	09	95	1.160	0.753	1.787	0.5009	247.932	•	3012.96	
SSTR4	G75	765	1501	2266	•	•	•	0.2827	•	0.7164	٠	0.6834
	G751	112	242	354	٠	٠	•	•	240.398	•	2987.89	
	G752	653	1259	1912	1.145	0.894	1.466	0.2827	238.788	•	2971.12	·